

CA1 HW 1178E21

Canada, DNHW, EHD,

78-EHD-21

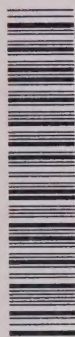
METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL (MMT).

1978.

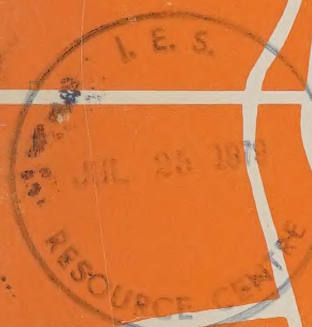
Health and Social Welfare
Canada

CA1 HW1178 E21

Methylcyclopentadienyl manganese tricarbonyl (mmt)



3 1761 05688775 5



INST. FOR ENVIRONMENTAL STUDIES
UNIVERSITY OF TORONTO



3 1761 03883025 3

DATE DUE

21 OCT 94

NOV 9 '94

NOV 29 '94

15 JAN 1995

31 JAN 1995

Return Material Promptly

Earth Sciences Library

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL (MMT)

An Assessment of the Human Health Implications of its Use
as a Gasoline Additive

Environmental Health Directorate
Health Protection Branch

Published by Authority of the Minister of
National Health and Welfare

78-EHD-21

**COPIES OF THIS REPORT
CAN BE OBTAINED FROM:**

Information Directorate,
Department of National Health and Welfare,
Brooke Claxton Building
Ottawa K1A 0K9

FOREWORD

This Report was prepared by staff of the Bureau of Chemical Hazards, Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare. Available information on Methylcyclopentadienyl Manganese Tricarbonyl (MMT) has been reviewed in order to evaluate possible adverse human health effects resulting from its use as a primary antiknock additive in gasoline. This review has been issued as an Environmental Health Directorate publication in anticipation that such a document will prove useful to other government agencies and private groups concerned with ambient air quality.

Acknowledgement is given to Miss M.E. Meek, the principal author, and to Dr. R. Bogoroch for contributing to the preparation of this Report. The provision of extensive information by the Ethyl Corporation is also greatly appreciated.

SUMMARY

At present, Methylcyclopentadienyl Manganese Tricarbonyl (MMT) is added to fuel oil to suppress smoke formation and to improve combustion; current usage of this additive in gasoline is believed to be quite limited. As the amount of unleaded fuel being produced increases, MMT is one additive being given careful consideration as a primary antiknock compound. This Report deals with the possible health implications of its widespread use in gasoline.

MMT is not manufactured in Canada at present. However, its increased use as a fuel additive could result in exposure of individuals involved in the refining and distribution of gasoline. It has been evaluated as safe for intact or abraded skin contact (NIOSH criteria); the American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV) is 0.1 ppm - "skin". The "skin" notation is intended to suggest appropriate measures for the prevention of cutaneous absorption, so that the TLV is not invalidated.

Exposure of the general population to MMT from its use in gasoline would be minimal, since very little (0.1 %) is emitted in the exhaust. The most significant environmental consequence of the use of MMT as a fuel additive is the resulting discharge of manganese to the air, since the principal emission product is Mn_3O_4 . Therefore possible health effects of an increase in atmospheric manganese levels are considered. The U.S. E.P.A. estimates that manganese concentrations under worst conditions would increase to less than $5 \mu g/m^3$ for a 24-hour averaging time. Review of available limited information on industrial and community exposure to manganese and results of studies in animals of chronic inhalation of manganese exhaust products leads to the conclusion that there is no evidence at present to indicate that expected ambient manganese concentrations would constitute a hazard to human health. Data on secondary effects of the use of MMT in gasoline (effects on other emissions and atmospheric reactions) are limited and contradictory; no conclusions can be made at this time about their possible health implications. Recommendations for research to allow a more thorough evaluation of the possible health effects of the use of MMT in gasoline are included.

TABLE OF CONTENTS

	<u>PAGE</u>
I INFORMATION - DATA REVIEW	1
A. IDENTITY, PROPERTIES, AND ANALYSIS	3
1. Physical and Chemical Properties	3
2. Analytical Methods	4
B. USE AND PRODUCTION	5
1. Use	5
2. Production	5
3. Accidental Spillage and Emergency Procedures	6
C. ENVIRONMENTAL INVOLVEMENT	8
1. Emissions of Manganese	8
2. Other Emissions	9
3. Atmospheric Reactions	9
D. OCCURRENCE, RESIDUES, AND CONTAMINATION - MANGANESE	11
1. Soil, Air, Water and Food	11
E. EXPERIMENTAL TOXICOLOGY - MMT	13
1. Metabolism	13
2. Acute Toxicity	13
3. Chronic Toxicity and Clinical Effects	15
F. HUMAN HEALTH EFFECTS - MMT	16
1. Acute Toxicity	16
2. Chronic Toxicity and Clinical Effects	16
G. PUBLIC HEALTH EFFECTS	17
1. Emissions of Manganese	17
2. Other Emissions and Atmospheric Reaction Products	24
II EVALUATION AND ASSESSMENT	25
A. RECOMMENDED EXPOSURE LIMITATIONS - MANGANESE	27
B. EXPOSURE LEVELS - MANGANESE	28
C. ASSESSMENT OF RISK	29
1. Occupational Exposure	29
2. Public Health Effects	29
D. RESEARCH NEEDS	31
III REFERENCES	33



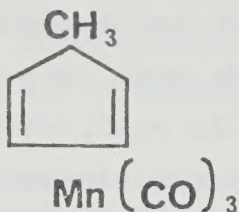
Digitized by the Internet Archive
in 2025 with funding from
University of Toronto

<https://archive.org/details/31761056887755>

I INFORMATION - DATA REVIEW

A. IDENTITY, PROPERTIES, AND ANALYSIS

A.1. Physical and Chemical Properties



Methylcyclopentadienyl Manganese Tricarbonyl
(MMT) (MCMT)
 $\text{C}_9\text{H}_7\text{O}_3\text{Mn}$ M.W. 218.1

Alternative Names: Manganese Cyclopentyltricarbonyl (MCPT),
Combustion Improver -2 (CI-2),
Antiknock -33X (AK-33X)

Appearance: orange liquid; faint, pleasant, herbaceous odor

Freezing Point ($^{\circ}\text{C}$)	-2.2	
Boiling Point ($^{\circ}\text{C}$)	233	
Melting Point ($^{\circ}\text{C}$)	1.5	
Flash Point (COC), ($^{\circ}\text{C}$)	93.3 ⁰	
Specific Gravity ($\text{H}_2\text{O} = 1$)	1.38	
Vapour Pressure (mm Hg)	20 $^{\circ}\text{C}$	0.051 mm
	25 $^{\circ}\text{C}$	0.1 mm
	61 $^{\circ}\text{C}$	1 mm
	100 $^{\circ}\text{C}$	9.3 mm
	160 $^{\circ}\text{C}$	100 mm
	233 $^{\circ}\text{C}$	760 mm
Solubility (25 $^{\circ}\text{C}$)	Water	70 ppm
	Glycerine	5 %
	N-Hexane	Miscible
	N-Heptane	Miscible
	Isooctane	Miscible
	Toluene	Miscible
	Ethanol	Miscible

Thermal Stability: decomposes very slowly at 200 $^{\circ}\text{C}$ and fairly rapidly at 300 $^{\circ}\text{C}$ in inert atmosphere; the presence of oxygen increases the rate of decomposition.

MMT is structurally similar to ferrocene, in that the methylcyclopentadiene ligand is π -bound to manganese. MMT is further classified as a penetration complex because dissimilar ligands are bonded to the manganese atom. The pure compound contains 25 % manganese by weight.

A.2. Analytical Methods

Analysis for MMT in gasoline or liquid fuels generally involves an atomic absorption spectrophotometric determination of manganese.⁽¹⁾

The U.S. National Academy of Sciences has suggested that procedures now being used for the determination of MMT in gasoline or liquid fuels might be modified to be suitable for its analysis in air.⁽²⁾ At concentrations above 0.1 mg/l, MMT in air has been determined in one study, by passage through fritted disc absorption towers containing glacial acetic acid and subsequent analysis for manganese by the periodate method.⁽³⁾ At lower concentrations, it has been determined by passage through absorption towers containing ethyl alcohol and analysis for manganese by the formaldoxime method.⁽³⁾

B. USE AND PRODUCTION

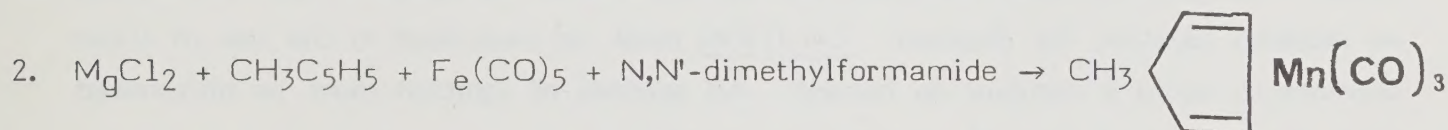
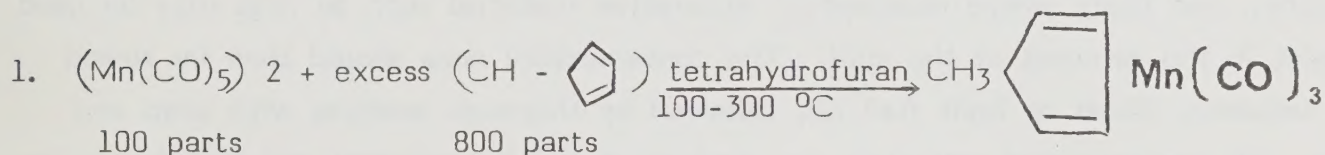
B.1. Use

Methylcyclopentadienyl manganese tricarbonyl is added to fuel oil to suppress smoke formation and to improve combustion. Typical treatment levels are 0.025 g of manganese per gallon of fuel oil for boilers and 0.08 - 0.5 g per gallon for turbines.

MMT is also used as an antiknock additive in gasoline. At a concentration of 0.125 g of manganese per gallon of gasoline, MMT provides, on the average, about 2 road octane numbers.⁽⁴⁾ While originally marketed in the late fifties and early sixties as a secondary antiknock for leaded fuels, it has been marketed since 1974 as a primary anti-knock additive for unleaded gasoline which is now required for cars equipped with catalytic converters. Current usage of this additive in gasoline is believed to be quite limited. As the amount of unleaded fuel being produced increases, MMT is one additive being given careful consideration as a primary antiknock compound. The maximum concentration of manganese in gasoline recommended by the Ethyl Corporation is 0.125 g per gallon.*

B.2. Production

MMT has been synthesized by several methods:⁽⁵⁾



Reaction 2 is carried out with the use of a Mn electrode, pressured to 1000 psi with CO₂; 25-30V and current density of 0.1 A/cm² at 195 °C for 3 hr.

MMT is not manufactured in Canada; it is produced only by Ethyl Corporation at a multi-products facility in Orangeburg, South Carolina. Production of MMT began in the late 1950's, reached and maintained a level of several hundred thousand pounds per year through most of the late 1960's and grew in the last few years to about 1,000,000 pounds per year. Most of the MMT marketed is used at present for smoke control in gas turbine generators.

*All gallons refer to U.S. gallons

1 U.S. Gallon = 3.785 litres = 0.8327 Imperial gallons

B.3. Accidental Spillage and Emergency Procedures

Procedures to be followed in the event of spillage or leakage, as recommended by the manufacturer are as follows:⁽⁵⁾

A spill or leakage of MMT should be reported immediately to Ethyl Corporation, Baton Rouge, Louisiana (Telephone 504-344-7147).

These procedures should also be closely followed:

1. Personnel

In case of contact, personnel should immediately remove all contaminated clothing while flushing the contact areas, e.g., skin and eyes, with plenty of water for at least fifteen minutes. The skin should then be washed thoroughly with soap and water. For eyes, get medical attention. Contaminated clothing should be removed to an isolated location for decontamination or disposal.

2. Clean-up in Open Areas

Maximum ventilation should be provided in the area of the spillage or leakage and personnel should avoid inhalation of MMT vapors. To avoid eye and skin contact, wear chemical splash goggles or face shield, polyethylene, neoprene or vinyl gloves and apron, and boots where necessary. Absorptive material such as rags may be used to assist in the removal of the spill. The contaminated area should then be rinsed with kerosene, diesel or light fuel oil, followed by thorough washing with soap and water. All contaminated materials and rinsings should be removed and transferred to an isolated location for disposal. CAUTION must be exercised in the use of these solvents to avoid a combustion hazard. All sources of ignition must be eliminated from the area until free of combustible vapors.

3. Clean-up in Confined Areas

If the MMT leakage or spillage is in a confined area, efforts should be made to provide adequate ventilation to the area with exhaust fans, etc. In addition, precautions should be taken during clean-up procedures, as described above, to avoid possible inhalation of lingering vapors. A FULL FACE PIECE CANISTER (ORGANIC VAPOR TYPE) MASK should be worn in a ventilated area. If good ventilation cannot be provided, AIR SUPPLIED RESPIRATORY EQUIPMENT must be used during clean-up procedures.

4. Decontamination Procedures - (To be conducted in an isolated area)

- a. Clothing - Contaminated clothing, other than leather goods, may be cleaned for reuse by rinsing in a solvent, such as kerosene, or preferably a non-flammable dry cleaning fluid, followed by thorough washing with soap and water. Shoes or other leather goods cannot be cleaned readily and should be disposed of by burning.
- b. Rags, rinsings, etc. - Contaminated materials should be burned or incinerated.
- c. Soil - For information on the disposal of contaminated soil, phone Ethyl Corp., Baton Rouge, Louisiana, 504-344-7147.
- d. Containers, equipment - All containers and equipment which have been in contact with MMT should be decontaminated in a manner similar to that described for clothing in item 4a. If absorbant material, such as wood, becomes soaked in MMT, it should be removed and burned. Containers must never be reused with any product intended for animal or human consumption.

C. ENVIRONMENTAL INVOLVEMENT

C.1. Emissions of Manganese

The most significant environmental consequence of the use of MMT as a fuel additive is the resulting discharge of manganese to the air. The principal emission product of combustion of methylcyclopentadienyl manganese tricarbonyl is considered to be manganous manganic oxide $\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}_2\text{O}_4$, generally represented as Mn_3O_4 . Mn_3O_4 is particulate in nature. Traces of manganic oxide (Mn_2O_3), and the uncombusted compound have also been reported to be present in the exhaust of test vehicles using gasoline with MMT. Typically, only about 0.1 % of the MMT is emitted from the tailpipe unburned; this trace of exhausted compound rapidly decomposes in sunlight to a mixture of manganese oxides and carbonates.⁽⁷⁾

A number of estimates of the increase in ambient levels of manganese expected to result from the extensive use of MMT in gasoline have been made. However, it must be emphasized, that, since current use of MMT is limited, estimates are based on models and these models cannot now be validated for manganese concentrations.

Based on the maximum concentration of manganese initially recommended for use in gasoline (0.125 g Mn/gal), the expected increase in concentration of manganese in the atmosphere has been calculated by the Ethyl Corporation by reference to literature data on lead in air.⁽⁷⁾ The levels of lead in air in the U.S. in 1969 varied from 0.00 $\mu\text{g}/\text{m}^3$ to 4.6 $\mu\text{g}/\text{m}^3$. At that time, lead was used in gasoline at a concentration of approximately 2.5 g/gallon (20 times the maximum recommended manganese concentration in gasoline). Assuming that manganese and lead emissions to the atmosphere are proportionate, Ethyl has concluded that manganese in air would therefore increase by a maximum of 0.25 $\mu\text{g}/\text{m}^3$ ($1/20 \times 4.6$) and that 90 % of sampling sites would be expected to have increases of less than 0.1 $\mu\text{g Mn}/\text{m}^3$. The median lead value for all urban sites in 1969 was 1.0 $\mu\text{g}/\text{m}^3$; therefore the predicted average increase in manganese would be 0.05 $\mu\text{g}/\text{m}^3$. It must be noted that this model is based on the assumption that the combustion characteristics of an alkyl lead compound (TEL) and an aryl manganese compound (MMT) are similar.

Manganese concentrations resulting from the use of MMT in gasoline have also been estimated by the U.S. Environmental Protection Agency.⁽⁸⁾ Estimates were made for various distances from the edge of a 2 -km section of a 6 lane highway based on available roadside measurements for lead and carbon dioxide; a proportionality factor was used for computing manganese concentrations. Based on these estimates it was concluded that the expected manganese concentrations under worst conditions (worst conditions likely to occur

only a few hrs./yr.) would be less than $5 \mu\text{g}/\text{m}^3$ for a 24-hour averaging time. It should be noted that the E.P.A. model predicted manganese concentrations 4 to 5 times higher than a similar Ethyl highway model.

A number of other estimates, also based on lead concentrations in ambient air, have appeared in the literature; the increase in atmospheric manganese, if MMT is used in gasoline at a maximum concentration of 0.125 g/gallon, has been estimated by one author to be $0.35 \mu\text{g}/\text{m}^3$ with a total yearly average of about 1.2 - 1.5 $\mu\text{g}/\text{m}^3$.⁽⁵⁾ Based on similar assumptions, it has also been stated that if all gasoline in California contained MMT at the maximum recommended concentration (0.0625 g/gal), the annual average contribution to urban airborne manganese concentration would be only 0.07 to 0.14 $\mu\text{g}/\text{m}^3$.⁽⁹⁾ The maximum monthly average manganese concentrations from MMT would be 0.09 to 0.38 $\mu\text{g}/\text{m}^3$.

C.2. Other Emissions

Besides the increased ambient levels of manganese that will result from the use of MMT in gasoline, a number of other environmental consequences of its use as a primary antiknock in gasoline have been identified:⁽¹⁰⁾

1. The use of MMT in gasoline appears to result in increased levels of total particulate that cannot be accounted for on the basis of increased manganese emission alone. Manganese also appears to have at least a minor effect on emitted particulate size distribution.
2. The use of manganese in gasoline appears to result in increased aldehyde emissions.
3. The effect of manganese on the emission of polynuclear aromatic hydrocarbons is not yet clear.
4. Manganese results in increased emissions of hydrocarbons; effects on carbon monoxide and nitrogen oxide emissions are less clear.

Available information on these effects is limited and often contradictory; further research is required before any conclusions can be drawn about secondary effects of the extensive use of MMT in gasoline.

C.3. Atmospheric Reactions - Catalysis of the Formation of Sulfur Trioxide from Sulfur Dioxide

Sulfur dioxide is emitted during the combustion of fossil fuels that contain sulfur as an impurity. SO_2 is considered to be a mild respiratory irritant; there is no evidence to suggest that it causes adverse health effects in man at concentrations present in urban air.

However, under conditions of high humidity in the presence of particulate material, sulfur dioxide is converted to sulfuric acid and particulate sulfates, compounds which are more irritating to the respiratory system than SO_2 itself. Manganese is one of the most effective catalysts for SO_2 oxidation.^(5, 11, 12) The rate of formation of H_2SO_4 triples when manganese concentrations double and increases linearly with an increase in SO_2 concentration.⁽⁵⁾

There is conflicting evidence in the literature about the efficiency, at various concentrations, of manganese as a catalyst for SO_2 oxidation. Estimates of the rate of atmospheric catalytic oxidation of SO_2 under similar environmental conditions and with similar concentrations of manganese vary considerably.⁽¹¹⁻¹⁴⁾

There is little information available on the efficiency of manganese as a catalyst for SO_2 oxidation at the ambient concentrations that are expected from the use of MMT in gasoline. To verify extrapolations from data in the literature on the effect of low levels of manganese in air on SO_2 oxidation, the Ethyl Corporation has conducted studies in a 3,500-ft³ black polyethylene bag with a controlled atmosphere containing SO_2 , water vapor, ammonia and exhausted manganese.⁽⁷⁾ In the absence of ammonia, the SO_2 reaction rate was unchanged with manganese concentrations of 4 $\mu\text{g}/\text{m}^3$. At very high concentrations of manganese (36 $\mu\text{g}/\text{m}^3$), no effect occurred below 70 % relative humidity and the oxidation rate increased rapidly only when the relative humidity was above 90 %. The addition of ammonia to the bag at 20 $\mu\text{g}/\text{m}^3$ more than doubled the rate of SO_2 conversion to SO_3 . These results suggest that the normal amount of ammonia in the air is probably the rate-controlling factor in atmospheric SO_2 oxidation and that the general use of MMT in gasoline would have little effect on the rate of SO_2 oxidation in the atmosphere. However, further data is required to validate these results.

The Calspan Corporation, under contract to E.P.A., has determined that, at manganese concentrations of approximately 0.5 $\mu\text{g}/\text{m}^3$, the presence of manganese had a measurable impact on visibility in a 20,000 cu ft chamber after 23 hours irradiation.⁽¹⁵⁾ However, this decrease in visibility cannot be attributed solely to the presence of aerosol sulfates.

D. OCCURRENCE, RESIDUES, AND CONTAMINATION - MANGANESE

Since the principal exhaust product of MMT is Mn_3O_4 , this section will summarize concentrations of manganese in the environment to place in perspective levels that can be expected from the extensive use of MMT in gasoline.

D.1. Soil, Air, Water and Food

Manganese does not occur naturally as a metal but is present in over 100 common salts and minerals widely distributed in rocks, soils and on the floors of lakes and oceans. It is most often present in the form of manganese dioxide, manganese carbonate and manganese silicate. It is invariably present in arable soil and is associated in trace quantities with every kind of plant and animal tissue.⁽¹⁶⁾ The average manganese content of Canadian soil is 800 ppm.⁽¹⁷⁾ Soil concentrations of manganese range from 0 to 7000 ppm.⁽¹¹⁾

Manganese is generally present in natural surface waters in dissolved and suspended forms in concentrations less than 0.05 mg/l. Data from Canadian national surface water stations indicate that only 3 areas recorded levels above 0.05 mg/l during the years 1974-1976.⁽¹⁸⁾ Higher levels of manganese in freely flowing river water are most often associated with industrial pollution. Higher levels are also found under reducing conditions such as exist underground or may occur in some lakes or reservoirs.

For sixty-seven percent of 84 national sampling sites for drinking water, manganese levels lie in the range of less than 0.01 mg/l to 0.02 mg/l. Levels in excess of the present Canadian limit in drinking water of 0.05 mg/l were recorded at 25 percent of the 84 national stations sampled.⁽¹⁸⁾

Manganese in the atmosphere is generated industrially, being emitted from various sources primarily as manganese oxides. The total estimated atmospheric emission of manganese in Canada in 1972 was 6625 tons; 99.4 % resulted from ferroalloy and steel production. Burning of coal for generation of electricity, burning of solid waste and sewage sludge in municipal incinerators and application of manganese containing fungicides constituted other significant sources of manganese emissions in Canada in 1972.⁽¹⁹⁾ The use of light and heavy oils in stationary sources was not a significant source of manganese emissions.

Analysis of air samples collected in the Montreal area in 1967-1968 shows values of approximately $0.03 \mu\text{g}/\text{m}^3$ for manganese content.⁽²⁰⁾ Slightly higher levels for the manganese content of air samples collected in various locations in Toronto have been reported. The manganese content of air samples in the vicinity of urban metal refineries averaged $0.062 \mu\text{g}/\text{m}^3$ (0.018 - 0.178). Manganese levels in samples from other areas in Toronto averaged $0.069 \mu\text{g}/\text{m}^3$ (0.038 - 0.166).⁽²¹⁾ These average values fall well within the range of manganese concentrations in air of areas, both rural and urban, considered by the U.S. Environmental Protection Agency not to be polluted by significant amounts of manganese emission.⁽⁸⁾ In the U.S., manganese concentrations in urban air average $0.10 \mu\text{g}/\text{m}^3$ and range as high as $10 \mu\text{g}/\text{m}^3$.⁽²²⁾

The manganese content of foodstuffs varies considerably. Generally, low concentrations are found in dairy (average $0.12 \mu\text{g}/\text{g}$) and meat groups (average $0.33 \mu\text{g}/\text{g}$). Manganese is relatively evenly distributed throughout all the food groups derived from plant sources (average $2.66 \mu\text{g}/\text{g}$).⁽²³⁾

It has been estimated that the average daily intake of manganese for Canadians is $2 \mu\text{g}$ through inhalation, $3600 \mu\text{g}$ in food and $40 \mu\text{g}$ in water.⁽²⁴⁾

E. EXPERIMENTAL TOXICOLOGY - MMT

The reported low emission rate and instability of MMT in the atmosphere suggest that exposure of the general population to the parent manganese compound in exhaust would be minimal. Sections E and F have been included to provide information about possible health implications for individuals engaged in the manufacture, distribution, blending, testing and use of MMT.

E.1. Metabolism

When methylcyclopentadienyl⁵⁴ manganese tricarbonyl was administered orally and intravenously to rats, most of the labelled manganese was rapidly excreted in the urine and feces.⁽²⁵⁾ Seventy-three percent of an oral dose of 2.5 mg MMT (0.625 g Mn) was excreted within 24 hours; 36 % of this amount was present in the urine. Such a high percentage in the urine is not typical of normal manganese excretion. Analysis of the urine and feces indicated that the MMT was metabolized and that the manganese was excreted in an inorganic form.

The liver, kidney and lungs contained the highest concentrations of manganese after MMT administration. The tissue distribution after a single oral dose was similar to that for manganese, except for the high concentration found in the lungs and abdominal fat.

In rabbits and rats exposed to MMT in dermal irritancy tests, most of the MMT absorbed into the system was rapidly excreted.⁽²⁶⁾

E.2. Acute Toxicity

MMT can be absorbed from the enteric tract, through the skin or through the lungs in sufficient amounts to cause serious illness and death in experimental animals. LD₅₀ values vary widely, depending upon the species, the route of administration and the diluent.⁽²⁷⁾ There is also a wide variation in mortality response to a specific dosage of MMT; however, exceptional range in individual susceptibility is not peculiar to this manganese compound but is characteristic of manganese toxicity in general.

The signs of illness resulting from the administration of lethal doses of MMT are similar in all species regardless of the route of absorption and consist of initial mild excitement and hyperactivity, tremors, severe tonic spasms, weakness, slow and labored respiration, occasional mild clonic convulsions and terminal coma. Animals given sublethal amounts exhibit similar but less severe manifestations and, after suffering temporary losses in weight, appear to recover completely in 2 to 6 weeks. Residual neurologic effects have

not been noted. The predominant pathologic changes are found in the kidneys and livers of experimental animals.⁽²⁷⁾ In animals dying from exposure to MMT, concentrations of manganese are elevated in selected tissues.⁽²⁸⁾

It should be noted that toxic effects of exposure to MMT are not the result of acute manganese toxicity since manganese toxicity occurs at much higher dosage levels and the pattern of hepatic lesions is markedly different from that seen in acute manganese toxicity.

(i) Oral

Oral LD₅₀ values for several species are summarized in Table 1.⁽²⁷⁾ Hysell et al (1974) reported the LD₅₀ of MMT administered orally to rats in Wesson oil to be 58 mg/kg,⁽²⁸⁾ which is well within the range of values reported in Table 1.⁽²⁷⁾

Table 1 - The Immediate Oral Toxicity of Methylcyclopentadienyl Manganese Tricarbonyl (from Ref. 27)

Species	Preparation Administered	LD ₅₀ as MMT mg/kg (95 % C.L.)	
		Male	Female
Guinea Pig	Undiluted	-	905 (500 - 1640)
Mouse	2 g/100 ml peanut oil	352 (222 - 558)	
Rabbit	10 g/100 ml peanut oil	-	95 (72 - 124)
Rat	Undiluted	70	8
Rat	2 g/100 ml peanut oil	176 (160 - 194)	96 (70 - 130)
Rat	2 g/100 ml peanut oil	38 (33 - 34)	23 (21 - 25)
Rat	5 g/100 ml peanut oil	24	24
Rat	10 g/100 ml peanut oil	33	35
Rat	5 g/100 ml kerosene	40	47
Rat	10 g/100 ml kerosene	40	80
Rat	10 g/100 ml kerosene	18 (11 - 24)	9 (6 - 12)
Rat	10 g/100 ml kerosene	24 (23 - 25)	17 (15 - 18)

(ii) Dermal

When MMT was diluted with peanut oil (10 g/100 ml) and kept in contact with the intact skin of rats for 6 hours, the calculated LD₅₀ was 665 mg/kg.⁽²⁷⁾

On the basis of direct dermal irritancy and cellular toxicity tests in rabbits, MMT has been evaluated as safe for intact or abraded skin contact (irritancy grade of 1 on a scale of 4, NIOSH criteria).⁽²⁹⁾

Various concentrations of MMT in gasoline (0.4 g/l, 2.4 g/l, 16 g/l) were applied for extended periods of time on the skin of rabbits and rats. No significant adverse effects attributable to MMT were observed in rats. At the higher concentrations, vacuolar degeneration of the liver and kidney was noted in some of the rabbits. The severity of these effects was greater in the group given the higher dose.⁽²⁶⁾

(iii) Inhalation

The one hour LC₅₀ for rats by inhalation has been reported to be 220 mg/m³.⁽²⁷⁾

E.3. Chronic Toxicity and Clinical Effects

Inhalation

In one study, young mature dogs, cats, rabbits, guinea pigs, mice and rats were exposed repeatedly (7 hours per day, 5 days per week for up to 30 weeks) to various concentrations of MMT in air.⁽³⁾ Exposure to levels of 14 - 17 mg/m³ produced mortality only in rats and mice but not in other species. All animals survived 150 daily exposures to 6.4 mg/m³ without significant effect or pathological change. Pathological changes resulting from the higher concentrations were observed primarily in the liver and kidneys. Two female beagle dogs survived 100 daily exposures to 12 mg/m³ without exhibiting any signs of illness or pathologic abnormalities. In general, animals dying during chronic inhalation exposure exhibited chronic bronchitis and peribronchitis. Interpretation of results in this experiment was complicated by the occurrence in some animals of occasional diseases presumably unrelated to the experimental procedure.

A number of additional studies to determine toxicological effects on experimental animals of inhalation of MMT vapour have been initiated.^(30, 31)

F. HUMAN HEALTH EFFECTS - MMT

F.1. Acute Toxicity

Improper handling of MMT resulted in contact on the hands and forearms of 6 individuals for 5 to 30 minutes. Exposure produced a variety of symptoms including metallic taste, headache, nausea and dyspnea; these symptoms disappeared within 2 hours. Two cases of more severe exposure (1 1/2 hours) resulted in high manganese (46 - 137 $\mu\text{g Mn/l}$) content of urine soon after exposure. Within 2 weeks, urine Mn was within the normal range of 2 - 3 $\mu\text{g/liter}$. None of the exposed men had significant symptomatology either initially or later. No change in physical or neurological examination was noted in any of the cases.⁽³²⁾

F.2. Chronic Toxicity and Clinical Effects

In 1971, the American Conference of Governmental Industrial Hygienists first established the present Threshold Limit Value for MMT of 0.1 ppm (0.22 mg Mn/m³).⁽³³⁾ Threshold Limit Values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day (8-hour workday) without adverse effect. The TLV for MMT carries a "skin" notation which is intended to suggest appropriate measures for the prevention of cutaneous absorption so that the threshold limit is not invalidated.

G. PUBLIC HEALTH EFFECTS

Exposure of the general population to MMT from its use in gasoline would be minimal, since very little (0.1 %) is emitted in the exhaust. Since the most significant environmental consequence of the use of MMT as a fuel additive is the resulting discharge of manganese to the air, this section deals mainly with possible health effects of an increase in atmospheric manganese levels.

G.1. Emissions of Manganese

(i) Manganese-Essentiality and Biological Role

Manganese is an essential element in animals and man. It is required as a cofactor in a number of enzymes; it is essential to arginase and alkaline phosphatase in the liver; it plays a role in the proper functioning of flavoproteins and in the synthesis of sulfated mucopolysaccharides, cholesterol, and hemoglobin; and it is implicated in carbohydrate metabolism, lipid metabolism, oxidative phosphorylation, growth, reproduction, and brain function.⁽²⁾ Recently its presence in drinking water has been inversely associated with cardiovascular mortality.⁽³⁴⁾

In animals, experimentally induced or naturally occurring manganese deficiency has resulted in the following: lack of growth, abnormalities of bone (deformities, dislocations, and perosis) and of reproductive function (ovarian dysfunction, testicular degeneration, poor lactation, frequent abortions, and high mortality among the young) and symptoms of central nervous system disturbance (lameness and stiffness of legs, ataxia, loss of equilibrium).⁽³⁵⁾ Although no specific syndrome in man due to manganese deficiency has been described, it has been suggested that there may be an association between manganese deficiency and a number of disorders such as anemia, bone changes in children, and lupus erythematosus.

Minimal human nutritional requirements for manganese have not been established. However, based on the fact that no manganese deficiency in humans has yet been documented and that the normal daily manganese intake ranges from 2 to 7 mg per day,⁽³⁶⁾ it is reasoned that the minimum daily requirement is probably less than 2 mg per day. It has been determined that a daily intake of 3 to 7 mg per day will give a body burden of 12 to 20 mg in a 70 kg man.^(2, 37)

(ii) Manganese - Metabolism

The main routes of absorption of manganese are the respiratory and gastrointestinal tracts; negligible absorption of inorganic manganese occurs through the skin.⁽³⁸⁾ Organically-bound manganese may be absorbed by the cutaneous route.⁽²⁾

There seem to be efficient homeostatic mechanisms which keep manganese concentrations in the body and in tissue relatively constant despite variations in the diet.⁽⁹⁾ Manganese in the body is regulated primarily by excretion rather than by both absorption and excretion. The primary mode of manganese excretion is via the gastrointestinal tract. After absorption, manganese accumulates in the liver from where it is rapidly excreted in the bile for eventual elimination in the feces. Some of the metal is excreted through the pancreatic secretions and some directly through the wall of the gut. Very little (0.1 - 2 %) is eliminated in the urine. In normal individuals the daily urinary excretion rate is 1 - 8 µg/l;⁽³⁹⁾ variations in dietary manganese have little effect on the urinary manganese excretion. However, Horiuchi and co-workers noted a parallel between the concentration of manganese in air and proportionately elevated levels of manganese in whole blood and urine of industrial workers.⁽⁴⁰⁾ Significant correlation also was observed between manganese content of urine and neurological findings in workers in whom manganese intoxication was recent. The excretion of manganese appears to occur in two stages: 30 % is eliminated with a halftime of 4 hours, the remainder with a halftime of 39 days.⁽²⁾

The biological half-life of manganese in man is influenced by a number of factors including the intake of manganese, the state of iron storage and the hemoglobin concentration. The presence or absence of other cations can also modify manganese excretion. For example, oral and intraperitoneal tracer studies have shown that, in weanling rats fed a low calcium diet, the excretion of manganese increased.⁽⁴¹⁾

The bones contain the highest concentration of manganese, about 25 % of the total body manganese.⁽⁴²⁾ Cotzias postulated that "each animal tissue contains a concentration of manganese which is almost characteristic of the individual organ and independent of the species of the animal with which the tissue has originated".⁽⁴³⁾ Generally, organs and tissues do not accumulate large concentrations of manganese.^(2, 8) However, wide variations of manganese concentration have been reported in the literature, especially for blood levels.^(2, 42) The normal blood manganese concentration is generally accepted as 20 - 100 µg/l.

According to Schroeder, manganese in man neither accumulates nor declines with age; it passes the placental barrier, is stored in the newborn and is present in milk.⁽⁴⁴⁾ Dobrymina and Davidjan on the other hand, report that most organs other than the liver show a decrease in manganese content with age.⁽⁶⁸⁾

Manganese accumulates in pigmented areas of the body (retina, dark hair, and skin) presumably through its little understood role in the metabolism of melanin and its precursors.⁽²⁾ Although the manganese content of scalp hair may not correlate with environmental levels,⁽⁴⁵⁾ elevated levels in chest hair may be of diagnostic significance.

It has been reported that in experimental animals, manganese accumulates to a greater extent in organs after inhalation than after ingestion, the principal sites of accumulation being the lungs, the small intestine, the liver, the kidneys, pancreas, brain, and muscle tissue.⁽⁴⁶⁾ However, this statement seems to be an oversimplified summary of studies in which mice inhaled manganese dioxide dust in concentrations averaging $8,910 \mu\text{g}/\text{m}^3$ every 2 hours for eight days (particle size less than 3 microns).⁽⁹⁾ Concentrations in most tissues or organs were increased in the inhalation series, compared to controls with similar oral intake of manganese. The major differences in tissue levels, which could possibly be due to local deposition, were found in the lungs and trachea. High concentrations possibly attributable to swallowing of particles, were also found in the stomach and small intestine.

(iii) Manganese Toxicity

Manganese is regarded as one of the least toxic elements. Chronic ingestion experiments in rabbits, pigs, and cattle at 1000 - 2000 ppm dose levels have shown no effects other than a change in appetite and reduction in metabolism of iron to form hemoglobin.⁽²⁾ The toxicity of manganese varies with the valence state, with the route of administration and, when inhaled, with particle size. To date there is no evidence of sex difference in susceptibility to inorganic manganese intoxication.

(a) Industrial Exposure

Inhalation appears to be the main route of absorption in cases of intoxication in man. According to Mena, who used radio-tracer methods, 60 to 70 % of inhaled manganese dust is swallowed and absorbed through the gut while the remaining particles of diameter size less than a few tenths of a micron diffuse across lung alveolar membranes and eventually enter into the systemic

circulation.⁽³⁷⁾ Cooper has stated that although definitive studies are not available, it is probably safe to assume absorption of 50 % or less for particles in the respirable range, i.e., below 3 micrometers in diameter.⁽⁹⁾

Toxicity in man is usually the result of chronic inhalation of high concentrations of manganese dusts from industrial sources.^(39, 47-52) In these cases, there is apparently no correlation between age, duration of exposure and onset of symptoms; symptoms differ considerably from case to case. Onset may occur as little as three months or as long as 20 years after exposure. The severity of the symptoms, however, often is proportional to the length and intensity of exposure. The principal effects of long-term occupational exposure to inorganic manganese compounds are the production of "manganese pneumonia" or pneumonitis⁽³⁸⁾ and more commonly, manganism.

Clinical signs of manganese pneumonitis are initially those of acute alveolar inflammation. Breathing is markedly labored and difficult, respiration shallow and gasping. Cough and expectoration are rare. The illness changes, however, after the third day from frank pneumonia to less well defined localization and discrete pleural involvement. Fatality can ensue from heart failure between the fifth and tenth day.⁽⁵⁾

The early symptoms of manganism include psychosis resembling schizophrenia. The onset of psychiatric symptoms is usually insidious and progressive. The first manifestations are subjective complaints of asthenia, anorexia, apathy, insomnia or somnolence and a decrease in the rate of performance of motor acts. These are followed by overt behavioural changes. The correlation between symptoms and histological pathology at this stage is obscure. Later symptoms reflect extrapyramidal disorders similar to Parkinson's disease, the neurological manifestations and biochemical alterations of which have been detailed by Cotzias et al.^(49, 53) Removal from exposure in the initial stages results in remission of symptoms. However, neurological damage is not reversible.

The lowest daily and total exposure level to manganese which will result in symptoms of toxicity in man has rarely been systematically determined. From a review of available literature on industrial manganese intoxication, it has been concluded that verified cases of neurological disorders have been observed in man after prolonged occupational inhalation of dusts containing over 5000 $\mu\text{g}/\text{m}^3$.⁽⁹⁾ Acute pulmonary disease has occurred in the same

dosage range. Another author has reported that manganese ore miners in Chile, Brazil, Morocco and South Africa, manganese steelworkers in Pennsylvania and manganese dry battery workers in Egypt and Great Britain have shown incidence of neurological disorders and respiratory disease at concentrations ranging from $5,000 \mu\text{g}/\text{m}^3$ - $60,000 \mu\text{g}/\text{m}^3$.⁽⁵⁾ The Threshold Limit Value for manganese and compounds (the airborne concentration to which it is believed that nearly all workers may be repeatedly exposed without adverse effect) is $5 \text{ mg}/\text{m}^3$ ($5,000 \mu\text{g}/\text{m}^3$).⁽³³⁾

(b) Community Exposure

There have been some reports in the literature on the influence of manganese emissions on inhabitants living in the vicinity of manganese industries. However, reliable data on concentrations of manganese present in the air of these communities is lacking and it is difficult, therefore, to draw conclusions about levels of manganese that have caused symptoms of manganese toxicity in the general population.

Increased incidence since 1939 of lobar pneumonia in Sauda, Norway, has been attributed to emissions of manganese from a ferromanganese smelting plant.^(54, 57) Post mortem examination of individuals who had died of lobar pneumonia in Sauda indicated that the manganese concentration in lung tissues was considerably higher than normal. As well, the rise in morbidity and mortality caused by lobar pneumonia paralleled the increase in the amount of ferromanganese discharged by the plant. The concentration of manganese in the atmosphere was reported to be a maximum of $64 \mu\text{g Mn}_3\text{O}_4$ ($46 \mu\text{g Mn}/\text{m}^3$) at a point 3 km from the plant. However, the method used to analyze for manganese was found to give low results and the total intake of manganese through inhalation is not known. Emissions from the plant also included other toxic compounds (dry matter in the smoke contained 54 % silica and 2.56 % manganese oxide near the plant).⁽²⁾

A similar situation in the vicinity of another ferromanganese plant in Aosta, Italy, in 1947, has been reported.⁽⁵⁸⁾ However, no quantitative data on the levels of airborne manganese present were included. The author of the report was also somewhat hesitant to attribute the increased pneumonia incidence in Aosta to manganese, in view of the fact that morbidity incidence decreased even though ferromanganese production continued.⁽⁹⁾

There have been a number of more recent reports from Japan relating pulmonary symptoms in children to increased manganese levels resulting from emissions from a ferromanganese plant.^(59, 60) However, the analytical data included in these studies are insufficient to determine critical exposure levels; most data were reported in terms of dustfall. Manganese dustfall measured monthly for 3 years averaged about 200 kg/km² per month in the vicinity of the plant, compared with 8 kg elsewhere in Kanazawa. Some 24 hour suspended particulate measurements made in the plant neighbourhood to 300 meters ranged from 4 to 260 µg Mn/m³. A comparative study of two groups of middle school students, investigating subjective symptoms, medical history, present condition and pulmonary function test by respirometer, indicated that students in a school 100 m away from the plant had a higher incidence of nose and throat symptoms, a higher history of pneumonia and lower pulmonary function than did students in a similar school remote from the manganese plant. A resurvey after controls were installed in the ferromanganese plant (manganese dustfall was reduced from 200 kg/km² to 20 kg/km²) showed that the health effects identified were mainly reversible; the prevalence of nose and throat symptoms in the polluted school decreased to a level comparable to that of the control school.

(c) Animal Models - Exposure to Manganese Aerosols

There are few reliable data on levels of manganese in air that have caused symptoms in man in community and industrial situations. However, several animal studies have been conducted to evaluate possible toxicity resulting from chronic exposure to manganese aerosols at concentrations approaching ambient levels expected from the use of MMT in gasoline as a primary antiknock agent.

The primary exhaust product of combustion of MMT, Mn₃O₄, is much less toxic than is MMT. Consumption by rats of from 4 - 8900 mg/kg body weight of Mn₃O₄ caused no mortality or apparent tissue damage.⁽⁶¹⁾ Even daily oral doses 150 times greater than the oral LD₅₀ of MMT to rats were only slightly toxic.

In rats and hamsters exposed for 56 consecutive days to irradiated and nonirradiated automotive emissions containing increased concentrations of manganese particulate (average, 117 µg/m³) resulting from the addition of MMT, no gross changes in general condition or appearance of the animals

were observed.⁽⁶²⁾ Microscopic examination of tissue revealed no changes which could be solely attributed to the presence of manganese or MMT. Nevertheless, manganese concentrations in several tissues from exposed animals were elevated significantly; the concentration of manganese in the brain tissue, liver and lungs of the exposed animals was on the average 1.8, 1.69 and 1.5 times the concentration in the respective tissues of the control animals.

In monkeys and rats exposed continuously for 9 months to a manganese oxide aerosol produced by combusting vapours of MMT (11.6, 112.5, 1152 $\mu\text{g}/\text{m}^3$ Mn), no apparent adverse effects were observed.⁽⁶³⁾ Body weights were not adversely affected by the exposure conditions; EMG and limb tremor evaluations were totally negative with respect to effects due to exposure conditions. Hematologic evaluations indicated an increase in hemoglobin and mean corpuscular hemoglobin concentration in the high level groups of both rats and monkeys as compared to the control group. However, the difference was small and the values remained within an acceptable normal range. There were no adverse effects in any of the serum biochemical parameters of either rats or monkeys. Tests of pulmonary function in monkeys were negative as regards adverse effects related to the exposure conditions. Tissue levels of manganese 6 months post-exposure were comparable for all groups in both monkeys and rats. There was some suggestion of slightly elevated lung weights for rats in the high level groups; however, this was probably related to higher body weights. Histopathological evaluations of either monkeys or rats failed to demonstrate any adverse effects which could be related to exposure conditions.

No toxic effects were observed in another study in which rhesus monkeys were exposed continuously for periods of up to 66 weeks to manganese oxide particulates (100 $\mu\text{g}/\text{m}^3$ Mn) generated through combustion of vaporized MMT.⁽⁶⁴⁾ There was small but statistically significant increases in manganese levels in the lungs, livers, pancreas, kidney and heart muscle. Also, concentrations were greater in the brain pallium, basal ganglia, cerebellum and pons. The data yielded no evidence of any alteration in the rate of fecal excretion of manganese induced by respiratory exposure to manganese oxide nor was there any change in the blood manganese levels elicited by exposure.

(iv) Manganese - Acceptable Daily Intake

According to Schroeder, no adverse health effects in humans have been noted with daily manganese intake levels as follows:⁽⁴⁴⁾

	<u>Average (mg)</u>	<u>Range (mg)</u>
Food	3.000	2.0 - 7.0
Water	0.005	0.0 - 1.0
Air	0.002	0.0 - 0.029

G.2. Other Emissions and Atmospheric Reaction Products

Since available information on the effects on other emissions and atmospheric reactions resulting from the use of MMT in fuel is limited and contradictory, no conclusion can be drawn about possible health implications of secondary effects of the use in gasoline of MMT as a primary antiknock additive.

A. RECOMMENDED EXPOSURE LIMITATIONS - MANGANESE

The Threshold Limit Value for manganese and compounds, established by the American Conference of Governmental Industrial Hygienists, is 5 mg/m^3 ($5000 \text{ } \mu\text{g/m}^3$).⁽³³⁾ Threshold Limit Values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effects. It is generally accepted that the TLV for manganese and compounds carries a low margin of safety for those occupationally exposed. Limits adopted in some other countries are lower ($0.3 - 5 \text{ mg/m}^3$). To date, there are no ambient air quality or stationary or mobile source emission standards for manganese.

B. EXPOSURE LEVELS - MANGANESE

Levels of manganese in the air of Canadian urban communities currently average less than $0.10 \mu\text{g}/\text{m}^3$.^(20, 21) The U.S. E.P.A. estimates that manganese concentrations resulting from the use of MMT in gasoline under worst conditions would be less than $5 \mu\text{g}/\text{m}^3$ for a 24-hour averaging time.⁽⁸⁾ Other authors give lower estimates; predicted average annual increases range from $0.05 - 0.35 \mu\text{g}/\text{m}^3$.^(5, 7, 9)

The average daily intake of manganese in air is, at present, considered to be $2 \mu\text{g}$. If MMT is used in the future as a primary fuel additive, daily intake of manganese from air would certainly not exceed and probably would be considerably less than $100 \mu\text{g}$, assuming the daily intake of air to be 20 m^3 .

Manganese intake is much greater from food than from inhalation or from ingestion of water. The daily dietary intake of manganese in typical Canadian diets has been estimated to be $4100 \mu\text{g}$ in the Ottawa-Hull area,⁽⁶⁵⁾ $3700 \mu\text{g}$ in Vancouver and $3000 \mu\text{g}$ in Halifax.⁽²³⁾ The average of these values, $3600 \mu\text{g}$, compares with the total dietary intake of manganese in food for the non-occupationally exposed individual in a non-polluted area estimated by Schroeder *et al.*⁽⁴⁴⁾ Generally, only 3-4 % of orally administered manganese is absorbed from the G.I. tract of healthy normal individuals.^(37, 67)

Assuming daily water consumption to be 2 litres and the average manganese content of Canadian drinking water to be $20 \mu\text{g}/\text{l}$, the average daily intake of manganese would approximate $40 \mu\text{g}$. There is considerable variation in such estimates, however. Craun and McCabe estimated the average daily intake of manganese from drinking water in the U.S. to be $44 \mu\text{g}$.⁽⁶⁶⁾ The U.S. E.P.A., on the other hand, considered this value to be $5 \mu\text{g}$.⁽⁸⁾

C. ASSESSMENT OF RISK

C.1. Occupational Exposure

Although MMT is not manufactured in Canada at present, its increased use as a fuel additive could result in exposure of individuals involved in the refining and distribution of gasoline. On the basis of NIOSH criteria, MMT has been evaluated as safe for intact or abraded skin contact.⁽²⁹⁾ The TLV recommended by the ACGIH is 0.1 ppm (0.22 mg Mn/m³) - "skin".

C.2. Public Health Effects

Based on the limited data available at present, there is no evidence to indicate that ambient manganese concentrations resulting from the use of methylcyclopentadienyl manganese tricarbonyl as a primary antiknock agent in gasoline (maximum 5 µg/m³ under worst conditions), would constitute a hazard to human health. Data available on other environmental effects such as catalysis of the formation of sulfur trioxide and effects on other emissions are limited and contradictory; no conclusions can be drawn about the possible health implications of such effects.

The paucity of available toxicological data does not permit the establishment of dose-response relationships for long-term inhalation of manganese in different animal species and man. It has been suggested that verified cases of neurological disorders and pulmonary disease in man have been observed after prolonged occupational inhalation of dusts containing over 5000 µg/m³ of manganese.^(5, 9) There have also been reports in the literature on the increased incidence of pneumonia and pulmonary symptoms in communities in the vicinity of manganese industries; however, the lack of reliable analytical data on levels of manganese present and the presence of other toxic compounds in the emissions preclude the estimation of manganese concentrations that have caused morbidity in the general population. It appears though, that the levels of manganese in the air of such communities were considerably greater than those expected from the widespread use of MMT in gasoline in non-industrial communities. However, it should be noted that there may be differences in the chemical form, particle size and solubility of manganese in industrial as compared to exhaust emissions.

There are no data available on the effects of chronic exposure to low concentrations of manganese on special groups such as pregnant woman, infants and those with minor respiratory ailments.

Because of the lack of relevant human data on the toxicity of manganese, several preliminary studies on the effects of manganese exhaust products following chronic inhalation exposure using animal models have been conducted. To date, there have been no apparent adverse effects observed in rodents and primates exposed for periods of up to 66 weeks to 11.6 - 1152 $\mu\text{g}/\text{m}^3$ of manganese, generated by combustion of MMT. Maximum concentrations of manganese expected under worst conditons from the use of MMT as a primary antiknock agent ($5 \mu\text{g}/\text{m}^3$) fall well below the lower limit of this range of concentrations.

D. RESEARCH NEEDS

Research in the following areas to allow a more thorough evaluation of the health implications of the use of MMT as a primary antiknock agent in gasoline is warranted:

1. Experimentation with test vehicles under controlled conditions to:
 - (a) determine maximum levels of manganese in air that can be expected from the use of MMT in gasoline;
 - (b) characterize more fully the physical and chemical properties of resulting manganese emissions;
 - (c) determine effects of the combustion of MMT in gasoline on emissions such as aldehydes, polynuclear aromatic hydrocarbons, carbon monoxide and nitrogen oxides;
 - (d) determine the catalytic efficiency of manganese emissions in the conversion of SO_2 to sulfuric acid and particulate sulfates.
2. Further toxicological data is required to:
 - (a) increase present knowledge of the absorption, transport, metabolism, localization and excretion of various manganese compounds in humans;
 - (b) determine effects of inhalation of manganese on special risk groups such as pregnant women, infants and those with chronic respiratory diseases;
 - (c) establish dose-response relationships for toxicological effects on animals of emissions of manganese from the combustion of MMT.

REFERENCES

1. Bartels, T.T. and C.E. Wilson. Determination of methyl cyclopentadienyl manganese tricarbonyl in JP-4 fuel by atomic absorption spectrophotometry. Atomic Absorption Newsletter 8:3 (1969).
2. National Research Council Committee on Medical and Biological Effects of Environmental Pollutants. Manganese. National Academy of Sciences, Washington, D.C. (1973).
3. Witherup, S; K.L. Stemmer, E. Larson and E.A. Pfitzer. The toxicology of methylcyclopentadienyl manganese tricarbonyl II Repeated inhalation exposure. Kettering Laboratory in the Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio. Preprint.
4. Faggan, J.E.; J.D. Bailie, E.A. Desmond and D.L. Lenane. An evaluation of manganese as an antiknock in unleaded gasoline. Ethyl Corporation (1975).
5. Piver, W.T. Potential dilemma: the methods of meeting automotive exhaust emission standards of the Clean Air Act of 1970. Environmental Health Perspectives 8:165 (1974).
6. Petroleum Chemicals Division, Ethyl Corporation. Product handling brochure "Ethyl" MMT. Ethyl Corporation.
7. Ethyl Corporation Research Laboratories. Methylcyclopentadienyl Manganese Tricarbonyl (MMT). An antiknock agent for unleaded gasoline. Status Report, Second Edition. Ethyl Corporation (1974).
8. U.S. Environmental Protection Agency. Scientific and technical assessment report on manganese. National Environmental Research Centre, Research Triangle Park. North Carolina, U.S.A. (1975).
9. Cooper, W.C. Airborne manganese and public health. Equitable Environmental Health, Inc., Berkeley, California (1977).
10. Moran, J.B. The environmental implications of manganese as an alternate antiknock. U.S. E.P.A. Research Triangle Park (1975).
11. Matteson, M.J.; W. Stober and H. Luther. Kinetics of oxidation of sulfur dioxide by aerosols of manganese sulfate. Industrial and Engineering Chemistry Fundamentals 8:677 (1969).

12. Cheng, R.T.; M. Corn and J.O. Frohlinger. Contribution to the reaction kinetics of water soluble aerosols and SO₂ in air at ppm concentrations. Atmos. Environ. 5:987 (1971).
13. Johnstone, H.F. and D.R. Coughanowr. Absorption of sulfur dioxide from air. Ind. Eng. Chem. 50:1169 (1958), cited in Calabrese, E.J. and A. Sorenson. Comment on methylcyclopentadienyl manganese tricarbonyl as an antiknock: Composition and fate of manganese exhaust products. J. Air Pollut. Control Assoc. 25:1254 (1975).
14. Wright, W.E.; G.L. Ter Haar and E.B. Rifkin. The effect of manganese on the oxidation of SO₂ in the air. Paper No. 74-198, presented at the 67th. APCA Annual Meeting, Denver, Colorado (1974), cited in Calabrese, E.J. and A. Sorenson. Comment on methylcyclopentadienyl manganese tricarbonyl as an antiknock: composition and fate of manganese exhaust products. J. Air Pollut. Control Assoc. 25:1254 (1975).
15. Calspan Corporation. A methodology for determining the effects of fuel and additive combustion products on atmospheric visibility. Draft Final Report. EPA Contract 68-02-0698 (1975), cited in Reference 10.
16. Rodier, J. Manganese poisoning in Moroccan miners. Br. J. Ind. Med. 12:21 (1955).
17. Warren, H.C. Some trace element concentrations in various environments. In Environmental Medicine. Edited by G.M. Howe and J.A. Loraine. William Heinemann Medical Books Ltd., London, England (1973), p. 9.
18. National Water Quality Data Bank. Inland Waters Directorate, Water Quality Branch, Environment Canada (1976).
19. Air Pollution Control Directorate. National inventory of sources and emissions of manganese. Environment Canada (1976).
20. Leroux, J. and M. Mahmud. Flexibility of X-ray emission spectrography as adopted to microanalysis of air pollutants. J. Air Pollut. Control Assoc. 20:402 (1970).
21. Jervis, R.E.; J.J. Paciga and A. Chattapadhyay. Assessment of public health hazards from urban metal refineries. Trans. Am. Nucl. Soc. 21:95 (1975).
22. Sullivan, R.J. Preliminary air pollution survey of manganese and its compounds. U.S. Dept. of Health, Education and Welfare (1969).

23. Kirkpatrick, D.C. and D.E. Coffin. The trace metal content of representative Canadian diets in 1970 and 1971. Can. Inst. Food Sci. Technol. J. 7:56 (1974).
24. Environmental Health Directorate. Manganese - drinking water criteria review. Health Protection Branch, Department of National Health and Welfare (1976). Preprint.
25. Moore, W.; L. Hall, W. Crocker, J. Adams and J.F. Stara. Metabolic aspects of methylcyclopentadienyl manganese tricarbonyl in rats. Environ. Res. 8:171 (1974).
26. Witherup, S.; K.L. Stemmer and E.A. Pfitzer. The toxicology of methylcyclopentadienyl manganese tricarbonyl III Effects resulting from repeated contact of the skin with gasoline containing MMT. Kettering Laboratory in the Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio. Preprint.
27. Witherup, S.; K.L. Stemmer, E. Larson and E.A. Pfitzer. The toxicology of methylcyclopentadienyl manganese tricarbonyl I Immediate toxicity. Kettering Laboratory in the Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio. Preprint.
28. Hysell, D.K.; W. Moore, J.F. Stara, R. Miller and K.I. Campbell. Oral toxicity of Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in rats. Environ. Res. 7:158 (1974).
29. Campbell, K.I.; E.L. George, L.L. Hall and J.F. Stara. Dermal irritancy of metal compounds. Arch. Environ. Health 30:168 (1975).
30. Tox - Tips 15-5. August, 1977.
31. Tox - Tips 16-21. September, 1977.
32. Ethyl Corporation Medical Department. Toxicology of Methylcyclopentadienyl Manganese Tricarbonyl (MMT) Ethyl Corporation (1974).
33. American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1976. ACGIH (1976).
34. Masironi, R. International studies on trace elements in the etiology of cardiovascular diseases. Nutr. Rep. Int. 7:51 (1973).
35. Ellis, G.H.; S.E. Smith and E.M. Gates. Further studies of Mn deficiency in rabbits. J. Nutrit. 34:21 (1947).

36. Pier, S.M. The role of heavy metals in human health. Texas Rep. Biol. Med. 33:85 (1975).
37. Mena, J. The role of manganese in human disease. Ann. Clin. Lab. Sci. 4:487 (1974).
38. Rodier, J. Manganese poisoning in Moroccan miners. Br. J. Ind. Med. 12:21 (1955).
39. Hine, C.H. and A. Pasi. Manganese intoxication. West J. Med. 123:101 (1975).
40. Horiguchi, K.; S. Horiguchi, K. Shinigawa, T. Utsunomiya and Y. Tsugama. On the significance of manganese in the whole blood and urine of manganese handlers. Osaka City Medical J. 16:29 (1970).
41. Lassiter, J.W.; W.J. Miller, F.M. Pate and R.P. Gentry. Effects of dietary calcium and phosphorus of ^{54}Mn metabolism following single tracer intraperitoneal and oral doses in rats. Proc. Soc. Exp. Biol. Med. 139:345 (1972).
42. Underwood, E.J. Trace elements in human and animal nutrition, 3rd edition. Academic Press (1971).
43. Cotzias, G.C. Manganese in health and disease. Physiol. Rev. 38:503 (1958).
44. Schroeder, W.A.; J.J. Balassa and I.H. Tipton. Essential trace metals in man: manganese. A study in homeostasis. J. Chron. Dis. 9:545 (1966).
45. Creason, J.P.; T.A. Hinnens and E.E. Bumgarner. Trace elements in hair, as related to exposure in metropolitan New York. Clin. Chem. 21:603 (1975).
46. Mouri, T. Experimental study of inhalation of manganese dust. Shikoku Acta. Med. 29:118 (1973), cited in Reference 35.
47. Schuler, P.; H. Oyanguren, V. Maturana, A. Valenzuela, E. Cruz, V. Plaza, E. Schmidt and R. Haddad. Manganese poisoning. Indust. Med. Surg. 26:167 (1957).
48. Suzuki, T. Manganese pollution of the environment. Indust. Med. (Sangyo Igaku - Japan) 12:529 (1970).
49. Cotzias, G.C.; P.S. Papavasiliou, J.P. Ginos, R. Steck, and S. Duby. Metabolic modification of Parkinson's disease and of chronic manganese poisoning. Ann. Rev. Med. 22:305 (1971).
50. Emara, A.M.; S.H. El-Ghawabi, D.J. Madkour and G.H. El-Samra. Chronic manganese poisoning in the dry battery industry. Brit. J. Indust. Med. 28:78 (1971).

51. Jonderko, G.; Kujawaska, and H. Langauer-Lewowicka. Problems of chronic manganese poisoning on the basis of investigations of workers at a manganese alloy foundry. Int. Arch. Arbeitsmed. 28:250 (1971).
52. Rosenstock, H.A.; D.G. Simons and J.S. Meyer. Chronic manganism. Neurologic and laboratory studies during treatment with levodopa. J. Am. Med. Assoc. 217:1354 (1971).
53. Cotzias, G.C.; P.S. Papavasiliou, M.H. Van Woert, and A. Sakamoto. Melanogenesis and extrapyramidal diseases. Fed. Proc. 23:713 (1964).
54. Wefring, K. Pneumonia in the area of the Sauda factories in Ryfytke. Tids. Norsk. Laeg. 49:553 (1929), cited in Reference 8.
55. Elstad, D. Observations on manganese pneumonia. In: Proceedings of VIII International Congress on Industrial Medicine. Leipzig, Thieme (1939), p. 1014, cited in Reference 8.
56. Elstad, D. Factory smoke containing manganese as contributing cause in pneumonia epidemics in an industrial district. Nord. Med. 3:2527 (1939), cited in Reference 8.
57. Riddersvold, J. and K. Halvorsen. Bacteriological investigations on pneumonia and pneumococcus carriers in Sauda, an isolated industrial community in Norway. Acta. Pathol. Microbiol. Scand. 20:272 (1943).
58. Poloveri, F. Bronchopneumonia and the production of ferromanganese. Med. Lav. 38:30 (1947), cited in Reference 8.
59. Nogawa, K.; E. Kobayashi, N. Sakamoto, T. Hukushima, A. Ishizaki, T. Makino, S. Kagamori, Y. Hiramaru, S. Kauno, T. Katou, K. Konogawa and S. Asami. Studies of the effects on the respiratory organs of air pollution consisting of dusts composed mainly of manganese (First Report). Jap. J. Pub. Health 20:315 (1973), cited in Reference 8.
60. Kagamimori, S.; T. Makino, Y. Hiramura, S. Kawano, T. Kato, K. Nogawa, E. Kobayashi, M. Sakamoto, M. Fukushima, A. Ishizaki, K. Kanagawa and S. Asami. Studies on the effects on the respiratory organs of air pollution consisting of dust composed mainly of manganese (Second Report). Jap. J. Pub. Health 20:413 (1973), cited in Reference 8.
61. Exon, J.H. and L.D. Koller. Effects of feeding manganese antiknock gasoline additive exhaust residues (Mn_3O_4) in rats. Bull. Environ. Contam. Toxicol. 14:370 (1975).

62. Moore, W.; D. Hysell, R. Miller, M. Malanchuk, R. Hinnars, Y. Yang and J.F. Stara. Exposure of laboratory animals to atmospheric manganese from automotive emissions. Environ. Res. 9:274 (1975).
63. Huntingdon Research Centre. Evaluation of the chronic inhalation toxicity associated with a manganese aerosol produced from the combustion of methylcyclopentadienyl manganese tricarbonyl. Final Report, Project Number 731-339. Ethyl Corporation, Baton Rouge, Louisiana (1975).
64. Coulston, F. and T. Griffin. Inhalation toxicology of airborne particulate manganese in rhesus monkeys. Institute of Comparative and Human Toxicology, International Center of Environmental Safety, Holloman Air Force Base, New Mexico, Contract Number 68-02-0710 (1976).
65. Meranger, J.C. and D.C. Smith. The heavy metal content of a typical Canadian diet. Can. J. Public Health 63:53 (1972).
66. Craun, G.F. and L.J. McCabe. Problems associated with metals in drinking water. J. Am. Water Works Assoc. 67:593 (1975).
67. Patty, F.A. Industrial Hygiene and Toxicology. Volume II. Interscience Publishers, N.Y. (1962), p. 1079.
68. Dobrymina, O.J. and L.G. Daidjan. Changes with age in the levels of Fe, Mn, Cu and Co in the organs of healthy man. Med. Z. Uzbek 12:47 (1969).

**RESOURCE CENTRE
INST. FOR ENVIRON'L. STUDIES
UNIVERSITY OF TORONTO**



